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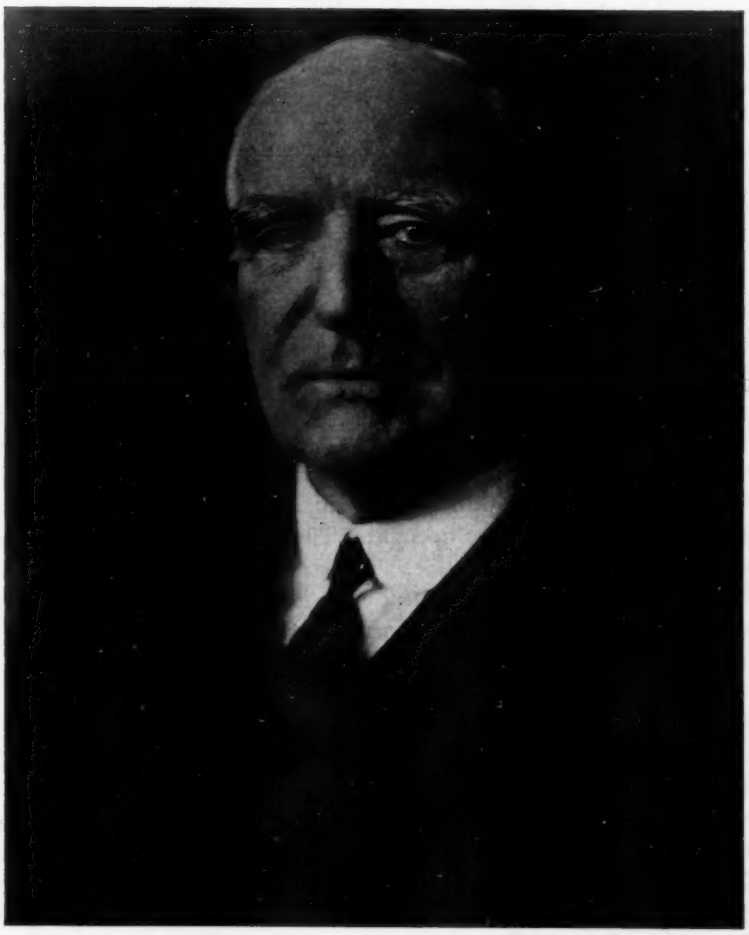
EDITORIAL

IN MEMORIAM



SIR HENRY S. WELLCOME

ALMOND, Wisconsin, in 1853, was a log-cabined hinterland, primitive and remote from the then existent seats of learning and of culture.

In a bare log cabin in this vicinity, some time during 1853, when lurking Indians still made life a misery for many a pioncer, Henry S. Wellcome was born. He was the son of an itinerant missionary, the Rev. S. C. Wellcome, who with his wife, Mary Curtis Wellcome, traveled through the Central States, in their covered wagon, bringing the word of God to Indian and to pioneer, and circulating, as was the custom of their day, a small collection of books and pamphlets, whose contents were eagerly consumed by a mind-hungry people.

After a long, diversified and serviceable career, that found him lifted to the eminences, and his name respected the whole world over, Henry Wellcome, the boy from Almond, Wisconsin, grown to Sir Henry Wellcome, of London, England, and a citizen of the world, passed away peacefully, in the eighty-third year of his age, on July 25, 1936.

When about five years of age he, with his parents and a party of several other families, migrated westward, trekking across the wild open country by day in covered wagons called prairie schooners; they halted, corraled and camped at night. Their destination was Garden City, a small but thriving frontier settlement in Minnesota, located between the Sioux and Winnebago Indian Tribes, in "the Land of Hiawatha," not far from "the Falls of Minnehaha, the merry laughing water," and near to the sacred Red Pipestone Quarry where the tribal pipes of peace were wrought. The environment was inspiring and primeval nature fair to see. The strenuous unconventional frontier life presented many delightful experiences and happy associations but also involved many severe hardships and grave difficulties which required the utmost fortitude to surmount.

Wellcome's primary education at Garden City was first in a typical frontier log schoolhouse, but as the pioneer settlement prospered, superior buildings were erected and higher grade schools established.

While still very young, a highly qualified English chemist came to Garden City, was appointed manager of a local pharmacy, and Wellcome, outside his school hours, received from him practical training in chemistry, pharmacy and materia medica, making such progress that when thirteen years of age he was appointed assistant dispenser.

His career in the field of public health, however, had already commenced, for as a boy of six, he had assisted his uncle, Dr. J. W. B. Wellcome, by holding a basin while the wounds of Minnesota pioneers who had been in battle with the Indians were being dressed.

When seventeen years old he entered the pharmacy of Poole & Geissinger in Rochester, Minnesota, where he worked from 1868 to 1871. It was there that he came under the notice of Dr. William Worrall Mayo, father of Dr. William J. Mayo and Dr. Charles H. Mayo, founders of the internationally famous Mayo Clinic. Sir Henry was a boyhood friend of the Mayo brothers, and this friendship was continued during his life.

The senior Dr. Mayo encouraged Sir Henry to study pharmacy and later arranged for his matriculation at the Chicago College of Pharmacy. During his attendance the Chicago fire destroyed the college, and he then enrolled at the Philadelphia College of Pharmacy. At the age of twenty-one he was graduated with his lifelong friend, Dr. Frederick Power, as members of the Class of 1874—in the days of Proctor, Maisch, Bridges and Remington.

The subject of his graduation thesis at the Philadelphia College of Pharmacy was on suppositories, in which he announced a new and improved shape. The new design received recognition in various textbooks on pharmacy. Since the shape of suppositories had come down through the centuries without change, the designing of a new and improved shape was an early indication of his creative instinct.

It may be said that his bent of mind towards originality played a very important part during later years in the development of his career.

At a gathering in Rochester in 1935, Sir Henry paid public tribute to the man who gave him his start. He said:

> "I owe whatever success I have attained to this world to Dr. William Worrall Mayo."

Following his graduation from the Philadelphia College of Pharmacy, Sir Henry spent a few years in the retail drug business in New York. Later he took a position with the firm of McKesson & Robbins, and as their representative traveled extensively throughout the United States and Mexico, finding time, however, to prepare for publication in the AMERICAN JOURNAL OF PHARMACY a number of scientific articles.

Sir Henry left New York for London, and in 1880 with the late Silas M. Burroughs established the firm of Burroughs, Wellcome &

Co., manufacturers of fine chemicals and galenicals. Mr. Burroughs died in 1895, and since that time Sir Henry served as the head of Burroughs, Wellcome & Co. In addition to the London organization, the firm has establishments in the United States, Italy, Canada, Australia, India, China, and other countries.

Sir Henry's American interests were wide and varied. He was a life member of the American Pharmaceutical Association since 1875, and always took an active interest in its scientific work. During the past several years he personally participated in the campaign for the establishment of a national headquarters building for the association in Washington. In 1934, when the Washington headquarters building was dedicated as the American Institute of Pharmacy, he was at the exercises. At this time he was the honorary president of the American Pharmaceutical Association and also was awarded the Remington honor medal for his scientific and other valuable contributions to pharmacy. In 1934 he received the honorary degree of Doctor of Science conferred by Marquette University, Milwaukee, Wisconsin.

For many years it was the custom of Sir Henry to spend a part of each year in Washington, where he was a member of the Cosmos Club, the National Geographic Society, the Archæological Society of Washington, and the Minnesota Historical Society of the District of Columbia. He also was an honorary member of the American Society of Tropical Medicine and an honorary member of the Association of Military Surgeons of the United States.

As a result of Sir Henry's experience and interest in tropical research, Secretary of War, the Hon. J. M. Dickinson, appointed him to visit Panama and make a survey of sanitary conditions and methods of operation in all sections of the Canal Zone, and to submit an unbiased report based on his personal observations. The report of Sir Henry's survey secured a free hand for General Gorgas in continuing his monumental sanitary work in Panama.

Sir Henry was one of the sponsors and a director of the Gorgas Memorial Institute of Tropical and Preventive Medicine in Washington, operating scientific laboratories at Panama for research work touching causes and prevention of tropical diseases.

During the childhood of Sir Henry, which was spent on the frontier settlements of Minnesota, his interest in archæological subjects had its inception and continued to develop and find expression in some of his larger undertakings which are well known to archæologists.

On one of his expeditions to the Sudan he discovered several prehistoric Ethiopian archæological sites in the Upper Nile region. Excavations here were carried out under his personal direction, including the supervision of a technical and administrative staff of twenty-five Europeans and more than 3000 native workmen. Professor G. A. Reisner, of Harvard University, writing of these researches, said:

> "The Excavations carried on by H. S. Wellcome have thrown unexpected light on early Ethiopian history in this region. For the first time, a scientific achaeological record has been made of a site in the interior of Africa."

As an early American pioneer Sir Henry lived on the frontiers of civilization and he came to know the American Indian intimately. He had great respect for this race and regarded the American Indians as the noblemen of God's primitive people. For many years he has taken a personal interest in the welfare of a tribe of Indians in Alaska. In 1887 he published a work of some 500 pages on these Indians under the title "The Story of Metlakahtla," which relates how this tribe of savages was transformed into peaceful and industrious tillers of the soil through education and the adoption of Christianity.

Sir Henry received world-wide recognition for his great services and princely contributions to science and medicine, for his interest in missionary enterprises and for his personal work in medical research and in the history of medicine and for his archæological and ethnological explorations and studies. His scientific achievements range from pioneering the use of aerial photography in the making of archæological surveys to the establishing of a number of research institutions.

Among his distinctions were the winning of the Royal Humane Life Saving Medal in 1885 and the founding of the Lady Stanley Maternity Hospital in Uganda, Africa, as late as 1927.

His interest in preventive medicine reached to all corners of the world. He was the founder of a publication trust fund under the control and direction of the Chinese Medical Association, to provide standard medical, surgical and clinical textbooks translated into Chinese at prices within reach of native students.

During the World War he placed his scientific institutions at the service of the British Government. He instituted a commission to improve design and construction of army ambulances. For use in Palestine and Egypt during the war he constructed, equipped and supplied for the British Army Medical Service a chemical and bacterio-

logical motor field laboratory. It was at this period he became a British subject by naturalization.

In 1928 the honorary degree of Doctor of Laws was conferred upon him by the University of Edinburgh. In recognition of his life's work and generous support of medical research he was knighted by the late King George V in 1932, and in 1936 was awarded the Croix d'Officier de la Legion d'Honneur by the French Republic. In 1936 the Spanish Republic awarded him the decoration of Comendador de la Orden de la Republica in recognition of his outstanding services to Spanish interests.

Apart from the experimental research laboratories of the establishments of Burroughs, Wellcome & Co., which have to their credit an immense number of important original researches, Sir Henry has established a number of scientific institutions which are co-ordinated and under separate and distinct direction, including the following:

The Wellcome Physiological Research Laboratories—London (1894);

The Wellcome Chemical Research Laboratories—London (1896);

The Wellcome Bureau of Scientific Research—London (1913); and the Museum of Medical Science (including Tropical Medicine and Hygiene, 1914), and the Auxiliary Entomological Research Laboratory at Claremont, Esher, Surrey—(1915);

The Wellcome Tropical Research Laboratories—Khartoum, Anglo-Egyptian Sudan, Upper Nile, Africa—(1901); and the fully equipped Auxiliary Floating Tropical Research Laboratory on the Upper Nile, and its tributaries—(1906).

In 1931 a new building occupying a site 225 feet by 135 feet was erected in London for the Wellcome Research Institution. The cornerstone was laid by the Rt. Hon. Lord Moynihan of Leeds, president of the Royal College of Surgeons of England. The new building furnished the additional accommodation required to co-ordinate and extend the activities of the Wellcome Chemical and Medical Research Laboratories and Museums.

As an energetic and public-spirited man, Sir Henry held memberships in numerous medical, archæological, geographic and similar soci-

eties. He also received many honorary degrees in recognition of his scientific achievements and public benefactions. The following is a list of his memberships, degrees and appointments:

1. Graduate in Pharmacy—Ph. G. (Philadelphia College of Pharmacy and Science.)
2. Master in Pharmacy—Ph. M. Honoris Causa. (Philadelphia College of Pharmacy, 1903.)
3. Fellow of the Society of Antiquaries—F. S. A.
4. Fellow of the Royal Geographical Society—F. R. G. S.
5. Fellow of the Royal Anthropological Institute—F. R. A. I.
6. Fellow of the Zoological Society—F. Z. S.
7. Honorary Fellow of the Royal Society of Medicine, London.
8. Honorary Doctor of Laws conferred by the University of Edinburgh.
9. Honorary Fellow of the Royal Society of Tropical Medicine and Hygiene, London.
10. Honorary Corresponding Doctor of the College of Medical Men of Madrid.
11. Past Honorary President of the American Pharmaceutical Association.
12. Remington Medalist (highest honor of Pharmacy).
13. Honorary Fellow of the Royal College of Surgeons of England—F. R. C. S.
14. Fellow of the Royal Society—F. R. S.
15. Member of the Executive Committee of the Governing Board, Gordon Memorial College, Khartoum, Egypt.
16. Member of Board of Directors of Gorgas Memorial Institute of Tropical Medicine and Hygiene, Washington, D. C., and Panama.
17. Honorary Vice-President of the Society for Nautical Research, London.
18. Member of Central Asian Society.
19. Member of Council of the Africal Society, London.
20. Officer of Order of Hospital of St. John of Jerusalem.
21. Life Member National Geographical Society, Washington, D. C.
22. Life Member Archaeological Society of Washington, D. C.
23. Life Member Minnesota Historical Society.
24. Life Member American Pharmaceutical Association.
25. Member American Oriental Society.
26. Freeman of the Ancient Worshipful Society of Apothecaries of the City of London.
27. Honorary Doctor of Science, Marquette University, Milwaukee, Wisconsin.
28. Croix d'Officier de la Legion d'Honneur (French Republic).
29. Comendador de la Orden de la Republica (Spanish Republic).

ORIGINAL ARTICLES

UNSUSPECTED COPPER IN DOMESTIC WATER SUPPLIES II

By David Wilbur Horn, Ph. D.

THE main purpose of this second paper[1] is to give a simple test for copper in drinking water,—a test so simple that it can be applied by an untrained person without the use of laboratory equipment or chemicals other than those readily available almost anywhere.

In the first paper[2] it was shown that copper had been found in unsuspected domestic drinking waters, in quantities in excess of the Drinking Water Standards[3] adopted by the United States Treasury Department, June 20, 1925 for drinking water supplied to the public by common carriers in interstate commerce. These Drinking Water Standards state: "Copper (Cu) shall not exceed 0.2 part per million." This statement has not since been changed, or recalled, so far as I am aware. It was further pointed out in the previous paper that the common feature observed in the domestic water supplies in question was the joint use of (a) a pump that pumps both water and air and that maintains a sufficient air pressure over the water to force the water throughout the piping system of the residence, and (b) a piping system of copper pipes.

As these pumping systems that pump both water and air and maintain them in contact are widely advertised and therefore perhaps widely used, it is important to have a simple test for copper, available to those who happen to have combined such a pumping system with an outfit of copper delivery pipes.

For copper in such drinking waters, the simple test the writer wishes to direct attention to is conducted as follows:

Fill a white enamel ware bucket with the suspected water. Holding a cake of "Ivory" soap (or probably any other white soap) in

[1] The main points of this article were presented at the September meeting of the "Municipal, State, and Federal, Food, Dairy, Drug and Health Officials", U. S. Custom House, Philadelphia, Pa., September 5, 1935.

[2] This JOURNAL, Vol. 106, p. 261, 1934.

[3] U. S. Public Health Reports, Vol. 40, p. 717, 1925. Reprinted in Standard Methods of Water Analysis, Amer. Pub. Health Assoc., 7th Ed., p. 136, 1933. In the 8th Edition of Standard Methods of Water Analysis (1936) the Drinking Water Standards adopted by the United States Treasury Department June 20, 1925, are not reprinted.

the hand, agitate the water with the soap until a blue color, if any, develops. One part per million of copper will develop an appreciable blue color in the water. As the writer has found more copper in water drawn from hot water lines than in that from cold water lines, it is better to test the water drawn from the hot water line and be guided by this result in any general conclusion concerning the presence of excess copper in the household supply. Water that has stood longer in the hot water line, (for example, over night) is likely to contain more copper.

This simple test rests upon two facts well known to chemists: (a) that copper soaps are quite insoluble, and, (b) that copper soaps are colored blue to greenish blue.[4] The soap precipitates the copper ion as a blue substance which enhances any blueness of the water previously due to the copper ion.

In my own experiments I have used white enamel buckets approximately 24 cm. (about 9½ inches) deep, approximately 29 cm. (about 11½ inches) across the inside at the top, filled with the water to a depth of approximately 19 cm. (about 7½ inches), and containing when thus filled approximately 10 liters (about 10½ quarts) of water. In earlier experiments the soap was used in cake form; in later experiments, in the form of "Ivory Snow" previously dissolved by warming in the proportion of 5 of soap in 100 of solution.

One part per million of copper is readily made evident by this soap test, either in diffused daylight or in the artificial light from a "G. E. Mazda" lamp. Under controlled conditions 0.5 part per million was detected by four different untrained observers. The controlled conditions referred to involved the use of a copper-free water for comparison; rain water was used for the controls. Water from municipal supplies at times contains copper added to control the growth of algae. In the experiments, a solution of copper sulphate crystals (previously repeatedly recrystallized) containing 3.93 grams in 100 cc. of solution was added in the needed amounts to a bucket of rain water, and mixing accomplished by pouring back and forth from one bucket to another.

One fact developed in these experiments was that 0.5 part per million of copper gave a distinguishably deeper blue when the amount

[4] "In washing with soap, this water colored the latter visibly greenish", wrote E. Reichardt regarding a water containing 0.8 to 7.2 ppm. copper. See *Archiv der Pharmacie*, **52**, p. 513, 1873.

of soap added to the water was just short of the amount of soap demanded by the soap-hardness of the water. In non-technical language, when soap was dissolved in the water to be tested until the water upon shaking in a clean bottle gave a lather that was permanent more than 5 minutes, then the tested water looked distinguishably less blue than when less soap was used. Therefore it is not desirable to use too much soap.

It might seem that a test for copper that only brought out unmistakably five times (or even two and a half times) the upper limit set by the United States Treasury Drinking Water Standard was not sensitive enough to help the layman who wished to use the test toward his own safety. Whether this is true or not hinges upon the reliability of the published standard of the United States Treasury Department and upon the applicability to the water supplies in point. If it is true, as I have been informed by letter, that "at the time these Standards were formulated . . . the committee being without definite data 'played safe' and set the amount(s) at 0.2 . . . parts per million of copper . . . ", then the layman may be quite satisfied with the soap test. When positive it unquestionably betrays *more copper* than was regarded in 1925 as tolerable, by experts who wished to "play safe" with respect to waters usually ingested infrequently by one and the same individual. To what extent, if any, copper may show cumulative action as a poison, the writer does not know. To what extent, if any, mild and insidious effects of chronic copper poisoning may escape attention or be misinterpreted, the writer does not know. When these matters are questioned, there may be testimony on both sides. But when there actually is evidence, the reasonable presumption is that an authoritative standard will be forthcoming with respect to copper in waters ingested by one and the same individual several times daily throughout a long period of time. The degree of safety with which some compounds of heavy metals may be taken internally varies considerably depending upon whether the doses are occasional, or, are continued over a long period (even though they be very small). There may be a dangerous logical fallacy in any reasoning that rests upon the whole, undivided and unqualified transfer of drinking water standards for water on interstate carriers over to waters consumed several times daily, week in and week out.

Summary

1. The finding of unsuspected copper in domestic water supplies that make use of combined air and water pumps along with copper pipes, is reiterated.

2. For such domestic supplies a simple test, taking advantage of the blue color developed when a white soap acts upon a water containing copper, is advised. In white enamel vessels, the blue color is appreciable with 1 part per million (0.058 grains per gallon); and the test may be made to detect half this amount of copper.

3. It is advised that this soap test be applied to water that has been retained in the hot water (copper) pipes over night, or over some other prolonged resting period.

4. Attention is called to the fact that there is a difference between intermittent dosage and long continued dosage, with salts of heavy metals. This difference suggests a logical fallacy in unqualifiedly transferring Standards for water on interstate carriers to domestic waters, consumed, as domestic waters are, several times each day over an extended period of residence.

POSITIVE REACTION OF GLASS UPON ORTHO-TOLIDINE

By David Wilbur Horn, Ph. D.

ORTHO-TOLIDINE and glass together can produce a yellow color, visually indistinguishable from the yellow produced when ortho-tolidine and "active chlorine" interact. Glass seems to acquire this power to produce yellow with ortho-tolidine through hydration. The safest plan in using glassware in the test for "active chlorine" is to introduce the ortho-tolidine reagent first into the glass vessel; if no yellow color develops within the time fixed for the test, the water to be tested may then be added.

The yellow color may be observed, for example, when 1 cc. of ortho-tolidine reagent is put into a bottle from which *dilution water* (therein sterilized in the autoclave for bacteriological purposes) has been poured out. The color develops fully if the bottle is rotated so that the reagent comes in contact with most of the inner glass surface. I observed this reaction when experimenting on the effect of added thiosulphate upon the bacteriological laboratory results in water samples from swimming pools.[1] The observation seems chemically in line with a fact noted previously by Mylius, namely, that pulverized glasses of various kinds give a positive (blue) reaction with iodo-starch.[2]

When the color produced in 1 cc. of ortho-tolidine reagent placed in a 4 oz. *Cleaneasy Sterilizer Bottle* (Whitall Tatum Co., Phila.) was compared in the Duboscq Colorimeter with permanent standards prepared for "active chlorine", the color from each of 10 bottles averaged the equivalent of 3.6 ppm. "active chlorine". The widest limits of variation observed among the 10 were the equivalents of 0.7 ppm. and 8.4 ppm. Whatever differences in yellow color resulted from the pH of these solutions, as compared with water-reagent mixtures as usually tested, were neglected. The color developed in these experiments faded with time, showing an average loss of 13% within an hour.

Pyrex bottles (8 oz. hexagonal *nursers*) treated similarly but with 2 cc. of ortho-tolidine reagent showed a color equivalent to 0.8 ppm. of "active chlorine".

[1] This JOURNAL, *104*, p. 651 (1932).
[2] *Ber. d. chem. Ges., 22*, p. 310 (1889).

Light and darkness, time of draining, repeated rinsing with tap water, rinsing with alcohol or formalin or hydrogen peroxide before rinsing with tap water, all seemed ineffectual toward blocking the subsequent activity of the glass surface toward ortho-tolidine reagent. Soaking with hydrochloric acid (10 cc. concentrated hydrochloric acid to 100 cc. water) for increasing lengths of time up to 6 minutes as a maximum, rapidly reduced to an inappreciable value the activity of the glass toward ortho-tolidine.

New, dry bottles, used just as delivered, were found to be active toward ortho-tolidine reagent. The average equivalent of the color for 24 of these (*Cleaneasy*) bottles was 0.6 ppm. with the widest limits of variation at 0.3 ppm. and 0.9 ppm. New, dry Pyrex bottles, used just as delivered gave no color with ortho-tolidine.

The 24 bottles just referred to were next carefully rinsed, drained, and then allowed to stand filled with water at ordinary temperatures for 2 days. At most, only an almost imperceptible activity was thus induced in them. When they were similarly prepared and allowed to stand 3 years, the water in them then showed on the average color equivalent to 0.2 ppm. of active chlorine. When subsequently rinsed, drained and heated in the hot air sterilizer for 1 hour, they no longer showed any reaction with ortho-tolidine reagent; whereas bottles (of the same kind of glass) that had been filled with water and autoclaved one-half hour at 15 pounds pressure, when subsequently tested, then rinsed, and drained, and then heated for one hour in the same hot air sterilizer for the same time all gave strongly positive color reactions with ortho-tolidine reagent.

It is necessary to note that Mylius did not use the starch iodide reagent commonly employed; but a mixture of pure starch with aqueous pure iodine solution, decolorized by a trace of very dilute silver acetate or silver nitrate solution—(so that the hydrogen iodide present was therefore combined). He had previously[8] convinced himself that hydriodic acid or its soluble salts were necessary to produce the blue color with starch and iodine. He concluded that glass acts upon iodine in the place of the alkali, producing iodide as in the reaction:

[8] *Ber. d. chem. Ges., 20,* p. 688 (1887).

$$6\,NaOH + 6I = 5\,NaI + NaIO_3 + 3\,H_2O$$

THE NEWER KNOWLEDGE OF THE HORMONES AND THE PHARMACIST [1]

By Aaron Lichtin, Ph. G.[2]

THE ISOLATION in recent years of several active principles from the ductless glands, believed to be pure hormones, and an increased understanding of the pharmacologic action of these substances, has stimulated the interest of medical men to apply them in practical therapeutics. It is obvious that if the pharmacist is to supply these products to the physician, he must have some understanding of their sources, properties, standards and therapeutic action.

The modern development of endocrinology, or the science of the ductless glands, has its beginning with the researches of the American-French physician and scientist, Brown-Sequard, and the French physician, Claude Bernard. Brown-Sequard, in 1857, showed that an animal whose suprarenals were extirpated would live for only a few days after the operation, but if the blood of a normal animal were injected into the operated animal, life would persist for a much longer period. He also developed and administered on himself injections of sex glands, basically consisting of testicular fluid, with reported beneficial results.

The endocrine glands include the pituitary or hypophysis, suprarenals, thyroid, parathyroids, thymus, pancreas, ovaries and testes. Scientists were not content, however, with the dried glands and fluids. They searched for the active principles responsible for the action of the glands. In 1897, Abel, the brilliant American investigator, isolated epinephrine from the suprarenals. E. C. Kendall, another American research worker, isolated thyroxin from the thyroid in 1915.

In the meantime a larger number of clinical observations were recorded dealing with the abnormal function of glands. Thus Frölich in 1901 showed that the anterior hypophysis was in some way related to the function of the sex glands and body structure. Erdheim and Stumme in 1909 observed the marked enlargement of the anterior hypophysis in pregnancy. Yet it was not until 1927 that Evans, Smith, and Engle in the United States and Aschheim and Zondek in Germany elucidated the relationship between the anterior hypophysis and sex gland function. It is evident from what has been stated that the rela-

(1) Presented at the meeting of the Pennsylvania Pharmaceutical Association, June, 1936.

(2) 1703 Pine Street, Philadelphia, Pa.

tion between observed facts and scientific elucidation made little progress until about 1930. Since that time, however, progress in this direction has been made rather rapidly. Through the researches of Evans, Smith and Engle, Aschheim and Zondek, Collip, Allen and Doisy and others, the anterior hypophysis was found to possess the following functions:

1. Growth producing: somatotropic.
2. Sex stimulating: gonadotropic.
3. Milk secretion stimulating: mamatropic.
4. Suprarenal stimulating: interrotropic.
5. Diabetogenic: carbohydrate metabolizing.
6. Ketogenic: fat metabolizing, increases acetone content of blood.
7. Thyroid stimulating: thyroidotropic.

In addition to the anterior part or lobe, the hypophysis includes in its structure a posterior part and an intermediary part.

The intermediary part, according to Zondek, possesses the property of pigment production, or is said to be chromatophorotropic. The posterior lobe possesses pressor, oxytoxic and anti-diuretic properties.

Now, let us consider the commercial products which are available on the American market to represent the various functions of this remarkable little gland.

1. The posterior lobe:

a. Solution of posterior pituitary, U. S. P. XI. One c. c. represents the oxytoxic activity on the isolated uterus of the virgin guinea pig corresponding to five milligrams of standard pituitary powder. This is equal to 10 units; therefore a unit of activity is equal to a half milligram, or to about 1/120 grain of standard pituitary powder. The standard powder is supplied by the Health Office of the League of Nations and is available in the United States from the U. S. P. office. Pituitrin O, or obstetrical, P. D. & Co., N. N. R. represents the U. S. P. article. It is marketed in 1 cc. ampules, each cc. containing 10 units.

b. Pituitrin S., surgical, P. D. & Co., is marketed in 1 cc. ampules, each cc. containing 20 units.

c. Pitocin, P. D. & Co., N. N. R. represents an oxytoxic activity of 10 units and a pressor activity of a half unit of pituitary per cc. It is marketed in 1 cc. ampules.

d. Pitressin, P. D. & Co., N. N. R. represents a pressor activity of 20 units and an oxytoxic activity of less than a half unit of pituitary per cc. In addition pitressin possesses antidiuretic properties. It is marketed in 1 cc. ampules.

2. The intermediate part:

At present there is no commercially available product of this part of the pituitary gland.

3. The anterior lobe.

The various functions of the anterior hypophysis are represented by the following commercially available products.

a. Growth producing.

Commercial products representing this property are:

1. Antuitrin-G., P. D. & Co., is marketed in 20 cc. rubber capped vials, 10 rat units per cc. A rat unit is defined as the minimum daily amount which, when injected intraperitoneally in two divided doses, will cause a daily average increase in weight of the experimental animal of one per cent. over a period of ten days. Antuitrin-G. is not strictly a pure fraction and may still be considered in its experimental stage. The dose is 1-3 cc., two to three times a week, preferably intramuscularly.

2. Anterior pituitary extract, Squibb, is marketed in 10 cc. vials containing 10 rat units per cc. It is not pure fraction and is said to contain in addition to the growth stimulating fraction, thyroid and sex stimulating substances. The dose is 0.5 to 5 cc. three times a week, intramuscularly.

3. Phyone, Wilson Laboratories, is marketed in 30 cc. rubber capped vials. It is claimed that its rat unit will cause an average daily increase in weight of 3 per cent. in the experimental animal, the albino rat. It also contains thyroid stimulating substance.

b. Sex organ stimulating or gonadotropic.

A few products relating to this function are obtained from the anterior lobe of the hypophysis, but the majority are produced from mare's pregnancy urine, placenta, amniotic, or fetal fluid, and by synthetic methods. The products obtained from the anterior lobe of the hypophysis are termed anterior pituitary substances, while those

obtained from other sources are termed anterior pituitary-like substances.

The anterior pituitary and anterior pituitary-like gonadotropic substances may be further subdivided according to the particular action they exert.

First: Sex stimulating in general, exerting a stimulating effect on both male and female sex organs.

Second: Ovarian-follicular stimulating or estrogenic, that is the effect which has to do with the stimulation of the menstrual cycle.

Third: Luteinizing, or that effect which has to do with the formation of the corpus luteum. The latter two effects can obviously be exerted only in the female.

Several anterior pituitary products exerting a general sex-stimulating effect are:

1. Gynantrin, Searle & Co., is marketed in 5 and 15 cc. rubber capped vials, each cc. containing 100 rat units. This manufacturer defines the rat unit as the smallest amount of the substance, which, when divided into six equal parts and injected into immature rats of a given age and weight over a period of three days, will on the fifth day produce sexually mature organs in 60 per cent. of the animals so treated. Dose, 0.1-2 c. c. intramuscularly.

2. Prephysin-Chappel, Chappel Bros., Inc., is marketed in 5 cc. rubber capped vials, each cc. containing 25 rat units. This product is standardized in a similar manner as Gynantrin. Dose, 0.5-1 cc. Caution as to overdosage is necessary.

Several anterior pituitary-like substances exerting a general sex stimulating or gonadotropic effect in both the male and female are:

1. Antuitrin-S, sexual, P. D. & Co., is marketed in 10 cc. rubber capped vials, each cc. containing 100 rat units. It is prepared from urine of pregnancy.

Antuitrin-S and products similar to it are generally evaluated by their ability to produce corpora lutea in the ovaries of immature rats under certain prescribed conditions.

2. Antophysin, Winthrop Chemical Co., is marketed in ampules containing a soluble powder equal to either 100 or 500 rat units, to-

gether with ampules of distilled water for dissolving the powder before injection. It is prepared from the urine of pregnancy.

3. A. P. L., Ayerst, McKenna and Harrison is marketed in 5 c. c. rubber capped vials, each containing, per cc., 100 "biological day units," which equal approximately 33 rat units. It is prepared from placenta.

4. Follutein, Squibb, is marketed in a syringe containing 1 cc. of a glycerine extract containing 1250 rat units, together with a 9 cc. vial of sterile water. The diluted material therefore contains 125 rat units per cc. Follutein deteriorates in about three weeks, and it is therefore best purchased on order. It should be stored in a refrigerator. Follutein is prepared from pregnancy urine.

5. Pitantrin, G. W. Carnrick, is marketed in 10 cc. rubber capped vials containing 100 rat units per cc. It is prepared from urine of pregnancy. All preparations in this group are administered intramuscularly.

Several anterior pituitary-like substances exerting a stimulating effecting on the ovarian follicle, and termed at times follicular hormones, are:

1. Theelin is a crystalline product obtained from the urine during pregnancy. It was first isolated by Doisy and his associates in 1929. Theelin is marketed by P. D. & Co. in 1 cc. ampules in either aqueous or oil solution; the aqueous solution contains 200 international units per cc., while the oil solution contains either 1000, 2000, or 10,000 international units per cc. The international unit is defined by the Permanent Commission on Biological Standardization of the Health Organization of the League of Nations as the estrus-producing activity of one ten-millionth of a gram of a standard preparation of theelin. By estrus is meant the phenomena which accompany the menstrual cycle; these include the follicular stage, ovaluation, if it occurs, luteinization and hemorrhage.

2. Theelol, P. D. & Co., is a preparation from the urine during pregnancy.

It is marketed in capsules for oral administration, each capsule containing the equivalent of either 1000 or 2000 international units. While theelin is chemically classified as ketohydroxyestrin, theelol is classified as trihydroxyestrin.

3. Progynon-B, Schering Corp., is marketed in oil solution, in 1 cc. ampules, each ampule containing 2500, 5000, 10,000, or 50,000 international units per cc. Chemically it is classified as the benzoate of theelol. It is injected intramuscularly.

4. Amniotin, Squibb, is marketed in ampules, capsules and pessaries. The ampules contain an oil solution of amniotin with a potency of either 2000 or 8000 international units per cc., for intramuscular injection. The capsules contain 1000 international units per cc. for oral administration. Amniotin pessaries are intended for vaginal administration and contain 2000 international units per pessary.

5. Emmenin, Ayerst, McKenna and Harrison, is prepared from placenta. It is marketed in solution for oral administration and is standardized in terms of day-oral units. A day-oral unit is about one-fifth of an international unit. Recommended dosage, 4-30 cc. daily.

6. Progynon, Schering, is an estrogenic preparation obtained from placenta and pregnancy urine. It is marketed in tablets and 1 cc. ampules. Each tablet contains 225, 1000, 2000 international units, while each ampule contains 125 international units in aqueous solution.

All estrogenic substances produce a cornification effect on the vaginal mucosa of the test animal and of the human being. Several anterior pituitary-like products which exert a stimulating effect on the corpus luteum, or luteinizing effect are:

1. Proluton, Schering Corp. This product is marketed in 1 cc. ampules containing 1/25, 1/5, 1/2, 1 and 5 international units per cc. The international unit represents 1 milligram of the crystalline hormone. The test animal for this and related products is the rabbit. The Corner unit is equal to the international unit, while the Clauberg unit is a half international unit.

2. Lipo-Lutin, P. D. & Co., is marketed in 1 cc. ampules, each cc. containing one international unit.

3. Progestin, Upjohn, is marketed in 1 cc. ampules, each cc. containing one international unit.

Luteinizing hormone is evaluated by its specific stimulating effect on corpus luteum formation subsequent to the administration of a definite quantity of estrogenic substance.

Testicular Hormones; Male Sex Hormones

Paralleling the hormones which the female elaborates in the ovary and corpus luteum, the male elaborates hormones in the seminiferous tubules and in the cells of Leydeg of the testes. Commercial testis hormones are, however, generally not prepared from the testis, but from male urine and, by synthetic methods, from sterols. It might be of interest to point out that there is a close chemical relationship between the hormones and sterols, the most familiar representative of the latter group being cholestrin, obtainable from wool fat. The commercially available synthetic products in this group are: Oreton or testosterone and Oreton-B or dihydroandrosterone benzoate. Both products are marketed by the Schering Corporation in oil solution in 1 cc. ampules, each ampule containing 2.5 milligrams of crystalline hormone. These products are evaluated by their ability to produce growth of the comb of a castrated cock or capon. Two and a half milligrams are equal to eighty capon units. A capon unit is defined as the minimum total quantity of hormone, which when injected daily for five days will produce growth of the comb of a capon 5 millimeters in length and thickness.

At the present time there are no commercially avaliable products to represent either the milk secretion stimulating, suprarenal stimulating, diabetogenic, ketogenic or the thyroid stimulating functions of the anterior pituitary gland.

The hormone of the thyroid gland is called thyroxin, and the dose is 1/300 to 1/30 grain.

Parathyroid extract, prepared by Lilly, Squibb and P. D. & Co, is commercially available in either 1 cc. ampules or 5 cc. rubber capped vials. The extract contains 100 units per cc. A unit is 1/100 of the amount of solution required to produce an increase of one milligram of calcium in 100 cc. of blood serum of normal dogs. The extract is administered either subcutaneously or intramuscularly, not intravenously. The average adult dose is 20-40 units every twelve hours for five or six days, never more than ten days in succession. Treatment should then be discontinued for a week or two, and may be resumed if necessary.

Insulin, obtained from the pancreas, is too familiar to most pharmacists, to require any comment. The unit of Insulin is based on the amount of the substance required to reduce the blood sugar of a rabbit,

under certain conditions. Protamine Insulin is a protein linkage Insulin, designed for slow absorption.

Eschatin, obtained from the adrenal cortex, is the newer product of the adrenals. It is marketed by P. D. & Co. in 10 cc. rubber capped vials. The product is evaluated by its ability to maintain life in adrenalectomized animals.

At present there are no commercially available preparations of the hormones of the thymus, or pineal glands.

Out of Order

"Many people are not really well all the time. It has been estimated that perhaps 10 per cent. are well, in the sense that their bodies are free from defects that alter function, and that they can carry on their affairs regularly, effectively, and comfortably, without let or hindrance because of aches, pains and ailments. The vast majority, perhaps 80 per cent., are from time to time, or even all the time, slightly or seriously, out of order in respect to health (e. g. subjected to repeated colds, indigestion, headaches, etc.; or lacking in the feelings and the appearance of genuine health). The remainder, 10 per cent., may be classed as frankly ill, either out of the running or badly in need of the curative ministrations of medical science.

"It is largely for these 80 per cent. who may be said to have a *subnormal health* that hygiene is of value."—F. L. Meredith in *Twelve Hours of Hygiene* (Blakiston's).

REPRINTED ARTICLE

THE EXTRACTION OF VEGETABLE MATERIALS*

Preparation of Drug Extracts and Tinctures

By W. C. Peck

[The following is an abstract of a paper read at the British Pharmaceutical Conference, held at Bournemouth on June 22-27, 1936]

THE extraction of vegetable drugs has been carried on for centuries, but examination of the published work on this problem reveals that little progress has been made for many years. This is probably because the fundamental principles have not received sufficient attention, with the result that many official formulæ are based on empiricism and tradition.

The acceptance of maceration and percolation as standard processes should be questioned in view of the conflicting published results. Recently the problem has been attacked from two different angles. Husa and co-workers [1] have studied the effects of the fineness of powder and variation in solvents on extraction of drugs, and the swelling, imbibition and penetration and the function of preliminary maceration with various menstrua. They concluded that fineness of powder is of small importance on extraction by percolation, and that there was no advantage in maceration before or after packing in percolators. In another direction Breddin [2] has evolved a new method of extracting drugs which is known as diacolation. The method consists of packing the powdered drugs into cylinders and driving the extracting liquid slowly by means of compressed air through one or more extraction vessels, the feature being that the solvent travels upwards. The method is essentially a more intensive displacement method and approaches quantitative filtration.[3] Twenty-four tinctures were prepared by Bari [4] by six different methods—maceration, double maceration, digestion, percolation, diacolation and heating on a water-bath. The products were compared and the best results for colour and clearness were obtained by percolation and diacolation; for total solid content, by percolation, diacolation and heating on a water-bath; for maximum amount of active ingredients, diacolation and percolation; whilst maceration gave lowest amounts. Comparative tests on tinctures made by maceration and diacolation, obtained better yields by

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the second method. The problem of drug extraction should, therefore, be examined more fundamentally, and it is necessary to survey the actual problem in detail in order to ascertain the exact steps that have to be undertaken in preparing drug extracts.

The Nature of the Vegetable Drug

Most vegetable drugs have been dried, and during the drying process many changes have taken place which must all be borne in mind. When a vegetable drug is dried, water is evaporated (1) from the cell sap, which results in the substances of the cell sap, in solution when the cell is alive, being precipitated or crystallised, or deposited in the cell as amorphous masses; (2) from the cell walls, which as a result lose their turgidity and so collapse, with the result that there is a decrease in size. When a dried drug, therefore, is immersed in pharmaceutical menstrua, hydration of the dried material takes place by means of imbibition and absorption. As a result, the drug increases in size. The swelling that occurs is greater across the grain than with the grain, and this is explained by the theories of cell wall structure. The conception of the cell wall, consisting of ultramicroscopic crystalline molecular complexes, which are called micellæ, arranged in spirals, is still the most satisfactory. Each micella is normally surrounded by a film of water, but in the dry condition the micellæ form a continuous membrane.

Koehler [5] holds the theory, which closely resembles that of Nagelli, that cell walls are made of ultramicroscopic fibrils which run spirally in the cell walls, and water is held almost entirely between these fibrils. These spirals usually run nearly parallel to the axis of the cell; as the water leaves the spaces between the fibrils they draw together in a direction almost at right angles to the axis. This action results in considerable transverse shrinkage, but slight longitudinal shrinkage. The characteristic component of the cell wall is cellulose. It is considered that the water causing absorption which invariably precedes swelling of cellulose affects the secondary valence.

Longitudinal swelling of cellulose fibres cannot occur to any extent, but the absorption of the hydroxyl containing molecules can affect the secondary valence and increase the distance between the parallel chains, causing swelling. Wood is made up largely of small cells, and the open spaces inside these cells are of the order of 0.01 mm. in diameter throughout most of their length, and perhaps much smaller

at the ends. They are small enough to act as capillary spaces and hold water at reduced vapour pressure. Hawley and Wise [6] conclude that water held in the microscopic cell cavities does not cause any swelling of the wood, for water entering a capillary is entering an existing space.

The theory of cell-wall structure, whereby molecules or small aggregates of cellulose in the cell wall are arranged in orderly pattern in parallel chains, explains the swelling whereby water absorbed enters into this arrangement of molecules in such a manner as to spread apart the chains of molecules and so produce swelling radial and tangential directions to the long axis of the fibre.

Water is much more strongly absorbed by wood than other volatile liquids. It has been stated that for sawdust the apparent maximum absorption was about 30 per cent., whilst with xylene and kerosene it was about 5 per cent.

Penetrability

The penetrability of wood has some bearing on the extraction of active principles. Most of the available data were obtained in experiments in treating wood with coal-tar creosote. It is concluded that there is only little correlation possible between penetrability and structure, but the penetration of creosote into wood is very much greater in the longitudinal direction than in either of the other directions, radial or tangential. The use of vacuum to increase penetration of the menstruum was suggested by Duffield,[7] who advocated that more perfect maceration could be obtained if the ground drug were placed in a strong cylinder, the air pumped out, and the requisite amount of menstruum admitted. He stated that "the pores of the comminuted drug give up the air enclosed in them, and when the menstruum is allowed to flow in, it is forced into these pores by pressure of the air outside."

The Preparation of Tinctures and Extracts

The preparation of tinctures involves:—

(1) Reduction of the drug to optimum particle size.
(2) The penetration of the ground drug by the menstruum.
(3) The solution by the menstruum of the physiologically active principles precipitated or otherwise deposited during the drying of the drug.

(4) Diffusion of the dissolved active principles through the cell wall into the menstruum surrounding the particle and establishment of uniform concentration.
(5) Separation of the menstruum from the marc.
(6) In the case of extracts, recovery by evaporation of the menstruum.

1. *Reduction of Particle Size.*—Reduction of the drug or vegetable matter has to be carried out either by grinding or some other process to produce particles of optimum size. In this connection McKinnis [8] has patented a process whereby leafy material, but not stems, barks, roots or seed, are prepared for extraction by conversion into coherent flakes of substantially uniform thinness, so that the soluble matter is readily accessible to the extracting fluid. Pressure is applied to the tissue to rupture the cells, and the mass may be pressed through heated rollers. The patent aims at reducing the diffusion of the soluble substance through the cell wall to a minimum by rupturing the cells, so that the bulk of the menstruum is in actual contact with the soluble material.

2. *Penetration of the Drug by the Menstruum.*—The advantage of the use of vacuum in the extraction of dried drugs in aiding the penetration by the menstruum has been demonstrated in the preparation of Tr. Gentian Co. and in the extraction of vanilla beans. The application of vacuum has two effects: (1) it withdraws all air from the finely divided drug so that the menstruum has a free entry; (2) on the vacuum being broken, the pressure of the atmosphere is used to force the menstruum into the drug. The preliminary moistening and maceration before packing into percolators has for its purposes, according to Couch [9]: (1) to assist in packing; (2) to allow modifications of the drug constituents; (3) to ensure saturation of every particle of drug with menstruum so that actual percolation may affect all the drug evenly.

The assistance in packing is, of course, to allow the drug to swell, and to allow for the even distribution of the very fine material. The preliminary moistening also functions to allow the escape of occluded air. When a small quantity of menstruum is used, this is absorbed and displaces the air, whilst when a large quantity is used and the drug particles are practically immersed, the air is locked up and so cannot escape.

Husa and Yates have reported that there was no advantage in vacuum maceration preceding percolation, but their figures show a slightly larger percentage with vacuum maceration.

3. *Solution of the Soluble Matter by the Menstruum.* 4. *Diffusion of the Dissolved Matter through the Cell Wall.*—The soluble matter is dissolved by the menstruum in two ways: (*a*) by direct solution of the matter from the ruptured cells; (*b*) from the unruptured cells by solution and diffusion through the cell walls. Prolonged maceration, once common before percolation, enabled the menstruum to dissolve the soluble matter and diffuse through the cell wall, and the percolation which followed was mainly to effect the separation of the menstruum from the marc and to wash the marc from strong menstruum. Maceration is a name for the procedure whereby solution and diffusion are carried out, whereas percolation is a name for a procedure whereby solution, diffusion and separation of the strong menstruum from the marc are carried out. The drug, during maceration, lies at the bottom of the menstruum, and each particle becomes surrounded with concentrated menstruum diffused through the cell wall, and so local equilibriums are set up which cause the solution and diffusion processes to cease. The surrounding menstruum is locked in by the mass of drug particles, and can only diffuse away to the rest of the solvent above, unless the whole is shaken. In a series of experiments it has been shown that the removal of the concentrated menstruum from the drug particles and its dilution and replacement with weaker menstruum greatly affects the rate of extraction of the drugs of Tr. Gentian Co. and vanilla beans. The introduction of stirring devices into the macerating liquid results in more rapid diffusion and solution, because the concentrated solvent passing through the cell wall is removed and diluted with weaker menstruum. It is probable that the cause of many discrepancies between reports on maceration and percolation processes is the amount of shaking given during the experiments.

In deciding on the best menstruum to use for the preparation of an extract for any drug, it is not sufficient to judge the menstruum on the analysis of the macerate or percolate, for the recovery of the solvent has an important bearing on the extraction. Husa and Huyet [10] have reported that the best results for the percolation of belladonna root are given with alcohol-water mixtures varying from 83.3 to 50 per cent. by volume of alcohol, but it is well known that in

the preparation of an extract of belladonna the lower the alcohol strength of the menstruum the greater the loss of alkaloids during the evaporation.

Large-Scale Extraction Plant for Vegetable Material

The imperfections of existing plant, *i. e.*, percolators, maceration vessels and presses, used for the carrying out of official processes for drug extraction are becoming evident. Plants are being designed to carry out efficiently the different physical and chemical operations involved in the separation of the physiologically active principles from the inert matter. They can be classified into several types, and operate with such varying degrees of efficiency that it becomes apparent that their design even now has also been based on empirical knowledge. In certain directions the influence of vacuum and of a circulating menstruum on the rate of extraction has already been recognised. No standard design, however, can be adopted for the extraction of all drugs because of their widely differing physical properties, such as swelling, penetration and the varying amount of fibre which aids separation of the menstruum from the marc.

Diacolation Plant.—An apparatus has been patented by Breddin, Brit. Patent No. 421,994, 1934, for extracting drugs by diacolation. The apparatus is shown in Fig. 1, and functions by driving slowly by

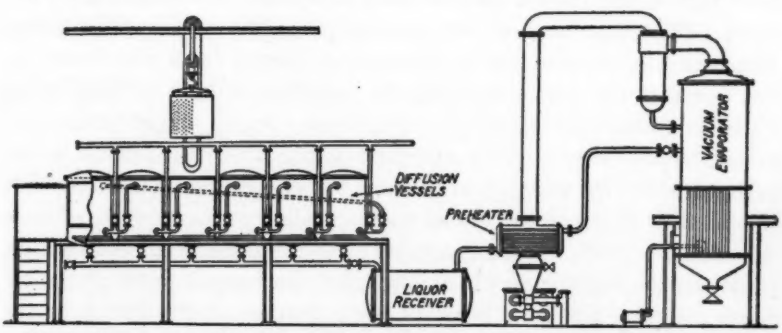

Fig. 1—Diagram of a Diffusion Extraction Plant Consisting of Six Diffusion Vessels.

means of displaced aid the extracting liquid through one or more extraction cylinders. It is provided with an adjustable throttle device between the supply container for the liquid and the first or only extraction vessel which is fitted with a dropping tube for indicating the rate of flow. Where a tincture is to be prepared, only one extraction

cylinder is employed, but for the preparation of extracts several cylinders in series are employed. The extraction liquid is forced from container by means of an air pump, through the throttle device comprising a rubber tube enclosing a wick or wad of thread and clamped between plates engaged by a pressure screw. The liquid then enters a float chamber, the float of which in the raised portion closes the outlet tube. The chamber communicates with a dropping inspection chamber, the drip tube carrying a check valve such as a rubber lip valve. From this inspection chamber the liquid enters the lower end of the extraction cylinder. The cylinder is packed with powdered drug and has filtering material at the lower and the upper ends. The liquid leaves by a tube passing through a rubber plug, which may extend into a plug which, with the filter material, forms a seal for the tube when not filled.

Diffusion Plant.—The upward passage of menstruum is not entirely new and has already been applied to materials which have a low resistance to flow, though Breddin's apparatus is designed to operate with materials which offer great resistance to the flow of the menstruum. A plant for this purpose consists of a battery of diffusion vessels, the number of which depends on the number of macerations necessary to exhaust the treated material. The vessels communicate with each other, the top of one being connected to the bottom of the next. The extraction of the material packed in perforated baskets systematically proceeds as the menstruum passes from maceration in one vessel to the next, displacing the menstruum there and becoming richer in extractive matter. The menstruum finally arrives at the end vessel, having been used for macerations in each of the vessels in the battery, whilst the material in the first vessel has been macerated with the number of charges of liquid corresponding to the number of vessels in the battery. The menstruum is then passed to an evaporation plant and the marc from the first vessel is discharged and replaced by fresh material, and now becomes, by operation of the valves in the connecting pipes, the last vessel.

This plant is designed to operate with water; however, when alcohol is used, a storage tank is installed so as to give the necessary head of pressure to work the plant. The alcohol, after passing through the battery, is run to receiving tanks and thence to a still for recovery. Agitators are sometimes employed in these extraction vessels, and

then the perforated baskets are dispensed with and the vessels are charged through doors in the sides.

Circulating Extraction Plants.—Extraction plants designed to exhaust by means of circulating the menstruum consist essentially of a cylindrical percolator with a perforated basket. The drug is packed into the basket in layers, being separated by perforated plates, and the menstruum is circulated by a pump through a spray nozzle on to the top plate. The plates eliminate channeling, and the menstruum collects in the bottom of the percolator and is then recirculated. A slight vacuum, about 2 to 4 lb., dependent on the nature of the drug extracted, is maintained underneath the basket, whilst a pressure of about 8 to 10 lb. is maintained at the nozzle.

The total solid content of the pressing liquor showed that equilibrium between the menstruum held by the drug and the free menstruum was established, and that extraction was completed. 40 lb. Rad. Gentian, ⅜ in. screen, 15 lb. Cort. Aurant Amar. Contus., ⅜ in. screen, 5 lb. Sem. Cardum Contus., No. 20 powder, were packed into the basket of a circulating percolator in 3-in. layers with 1-in. air space separated by perforated plates.

Extractors Operating by Repeated Distillation of the Solvent.—Where the solvent used for the extraction of a drug has a short boiling range and the extracted material is unaffected by prolonged heat, the total volume of the solvent used can be greatly restricted by dis-

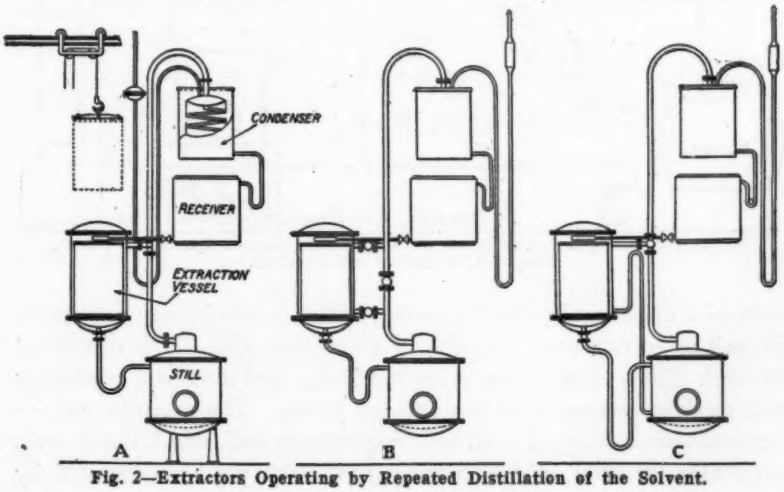

Fig. 2—Extractors Operating by Repeated Distillation of the Solvent.

tilling the solvent and allowing it to flow continuously over the drug. During its passage it extracts the soluble matter from the drug, and on passing to the still these extracted materials are left behind, and the solvent distilled back to the drug. This circulation continues till all the soluble matter is transferred from the drug into the still.

The plants shown in Fig. 2 show three variations in the design of plant of this character. They are: (*a*) where the solvent is condensed and flows downward through the drug to the still in a continuous stream; (*b*) where the solvent as vapour passes upward through the drug, and being condensed in the reflux condenser, travels downwards again through the drug back to the still; (*c*) where the solvent is condensed by the reflux condenser and flows into the drug where, after a maceration period, it returns by a syphon tube to the still.

Vacuum Agitating Extractors.—This class of extractor proves to be very rapid in operation. The plant is shown in Fig. 3 and con-

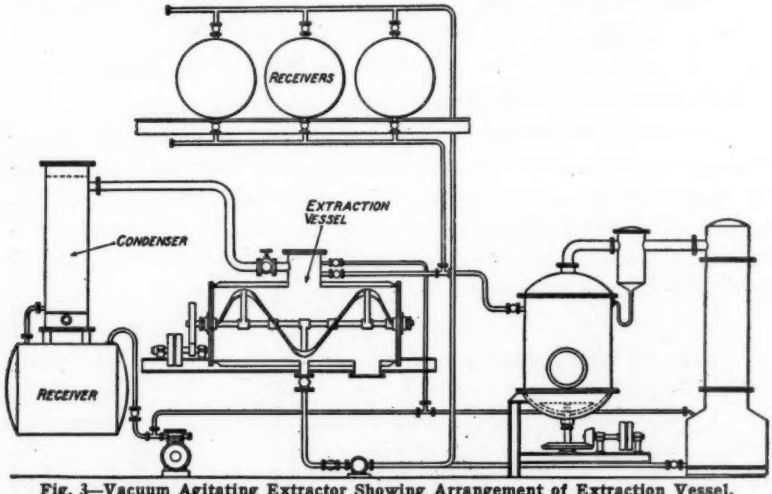

Fig. 3—Vacuum Agitating Extractor Showing Arrangement of Extraction Vessel, Receivers, Condenser and Receiver.

sists of a cylindrical jacketted vessel, with a powerful agitator which is used as an extractor and also as a recovery still. It is connected through filters to percolate receiving tanks, and also to a condenser and receiver connected with a vacuum pump. The percolate receiving tanks are connected to an agitating vacuum still, which has its own condenser, receiver, and vacuum pump. The plant is operated by

charging the drug into the extractor which is then evacuated, and the solvent introduced. The agitator is run for a short period and the mass thoroughly mixed under vacuum. The air is then allowed to re-enter the vessel and the percolate run off to receiving tanks. A series of washes is run through in this manner, so that a charge of percolate can be used to extract two or three charges of drug. The strong percolate is then run to the vacuum still and the solvent recovered; when a thick extract is obtained the agitator is stopped and a high vacuum held on the still and the still allowed to cool. The extractor so treated swells to a spongy material and, when cold, breaks up easily into a light powder and is run from the still. The exhausted drug in the extractor is freed from solvent by heating by the steam jacket, with the agitator running under vacuum, the solvent being condensed in the condenser and receiver provided for the purpose. This last plant is the only one of the type which carries out the total operations of preparing a pharmaceutical extract, that is, it (*a*) extracts the active principles; (*b*) separates the menstruum from the marc; (*c*) evaporates the menstruum to an extract and recovers the solvent; (*d*) recovers the solvent adhering to the marc.

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SCIENTIFIC AND TECHNICAL ABSTRACTS

Compiled by Linwood F. Tice, M. Sc.

Biological Investigations with Parahydroxybenzoic Acid Esters. H. Cremer. *Ztschr. Unters. Lebensm. 70,* 136 (1935), through *Pharm. Zent. 77,* 446 (1936). In order to determine whether the esters of parahydroxybenzoic acid had any injurious effect upon the vitamin content of various plant juices a series of animal experiments were conducted in which vitamin C was evaluated using guinea pigs, vitamin A using young rats, and vitamin B using pigeons.

A mixture of "Nipasol" (propyl parahydroxybenzoate) and "Nipagin" (methyl parahydroxybenzoate) was employed and it was found that the vitamins were not affected in the slightest. In fact the vitamins were protected from deterioration. The esters were without influence on the growth and weight of the animals, their general resistance to infection remained unchanged as did their blood pictures. No change in the animals was noticed in regard to metabolic rate or fertility. As a result of these experiments such esters are considered quite suitable for the preservation of vitamin-containing material.

"Antirancidol"—Drug and Cosmetic Industry 39, 113 (1936). Decomposition of vegetable and animal products in cosmetic preparations can take place in either or both of two ways. Bacterial action will cause a breakdown of the oil or fat, but this can be overcome by the use of a suitable preservative. The other type of action is oxidation and it is often overlooked. In this case, the compound or the free fatty acid take up oxygen and are transformed into materials bestowing rancid properties. Antioxidants overcome this difficulty with varying degrees of success.

"Antirancidol" is being offered as an antioxidant by the R. F. Revson Co. of New York. It is a light cream-colored powder with an aromatic odor which does not affect the odor of the finished product. Although it is not suggested for use in food preparations, the product is claimed to be non-toxic and non-irritating. It will dissolve in either water or oils in sufficient amounts to be effective. From 0.015 to 0.03

per cent. of "Antirancidol," based on the weight of the finished product, is usually adequate for protection against oxidation.

Addiction and Tolerance to Barbiturates. The Effects of Daily Administration and Abrupt Withdrawal of Phenobarbitol-Sodium and Pentobarbital-Sodium in the Albino Rat. E. J. Stanton. *J. Pharmacol. & Exper. Therap.* 57, 245 (1936). Since the introduction of barbital in 1903 and a multitude of analogous derivatives of barbituric acid subsequently, indiscriminate use by the public has led to an increasing number of reported cases of habituation with either acute or chronic poisoning as the ultimate result. Few data exist, however, concerning the occurrence of true addiction to these compounds in the sense of hyperirritability and other abstinence symptoms following their withdrawal.

The author carried out a series of experiments on albino rats, using two members of the barbituric acid series: phenobarbital-sodium, an example of a long acting barbiturate; and pentobarbital-sodium, an example of a short acting hypnotic.

The method utilized was a determination of the twenty-four-hour abstinence irritability of the rat receiving daily injections of the drug, irritability being objectively measured by recording the struggle response of the rat to a uniformly uncomfortable situation. Tolerance by this method is indicated by a progressive weekly increase in the level of response one hour after injection of the drug. Such an increase indicates a lessened tranquilizing power of the drug and hence a tolerance on the part of the animal.

The results show that following daily injection of both compounds there was no increase in abstinence irritability. On the contrary, the irritability progressively decreased especially with the larger doses and this extended to a considerable degree into the withdrawal period. Rats therefore do not become addicted to phenobarbital-sodium or to pentobarbital-sodium in the sense of increased irritability following withdrawal of the drug, but tend rather to show evidences of some cumulation of depressive effect.

The courses of injections induced only a very minor degree of tolerance to the maximal effects of pentobarbital-sodium as indicated by the struggle response of the rats one hour after injection, but the

duration of the somnifacient action appeared to be markedly shortened at the end of the injection period.

A New Michrochemical Reaction for Cantharidin. G. Deniges. *Bull. Soc. Pharm. Bordeaux 73,* 7 (1935), through *Quart. J. Pharm. and Pharmacol. 9,* 114 (1936). A few small particles of the substance to be tested are placed on a glass slide and moistened with a drop of a strong solution of ammonia. The mixture is gently dried by passing the slide over a small flame. The residue has a characteristic microcrystalline appearance. At the edges of the mass the crystals are long flat pyramids with quadrangular bases, the remainder consisting of plates and groups of tapering crystals terminating in a point. By sublimation of the residue and crystallizing of the sublimate from benzene, the characteristic microscopic crystals of cantharidin may be obtained.

The Use of Semi-Solid Agar for the Detection of Bacterial Motility. B. P. Tittsler and L. A. Sandholzer. *Jour. Bact. 31,* 575 (1936). The hanging-drop method for the detection of bacterial motility can be employed successfully, but it has several distinct disadvantages. It is so tedious that the determination of this bacterial characteristic is frequently neglected in the routine laboratory. Furthermore, the results are often uncertain because it is difficult to observe motility when only a few of the cells in a culture are motile. Finally, it is necessary to provide relatively young cultures for the examination.

The use of semi-solid media for the determination of bacterial motility, on the other hand, eliminates the shortcomings of a hanging-drop technic. The results are macroscopic and cumulative, thereby particularly qualifying the method for use in the routine laboratory, where examinations cannot always be carried out at a specific time. Moreover, this method practically eliminates the possibility of overlooking motility when only a small proportion of motile cells are present, because the localized outgrowths, which occur wherever motile cells are deposited along the stab can hardly escape notice.

Various workers have employed semi-solid media in the study of bacterial motility. The present authors report the results of a comparative study of bacterial motility using the hanging drop and stab culture methods on a long series of cultures involving more than 60 species of organisms. The semi-solid medium used was composed of 0.3% meat extract, 0.5% peptone and 0.5% agar. It was adjusted to pH 6.8 to 7.2 and dispensed in culture tubes finally sterilized in the autoclave. Inoculations were made by the stab method with a straight needle. The source cultures were on agar slants or in broth. Incubation was carried out at 37° C. for 6 days unless positive results were produced sooner. Hanging-drop preparations were made from either nutrient broth or 2% peptone water cultures incubated at 37° C. for from 8 to 10 hours; 12 to 15 hours, and 18 to 24 hours. In the semi-solid agar, motility was manifested macroscopically by a diffuse zone of growth spreading from the line of inoculation.

After incubation for one day in semi-solid agar, the results agreed with those of the hanging-drop method for 99.2% of the cultures. Ultimately, every culture which was motile in hanging-drop preparations was motile also in the semi-solid agar. In the case of 22 strains of the Escherichia-Aerobacter group, however, it required two days to elicit a positive reaction by the semi-solid agar method. On the other hand, most of the positive reactions were evident after from 8 to 16 hours. The fact that 20 strains of the Escherichia-Aerobacter group, and one spore-forming culture were definitely motile in semi-solid agar, but not in hanging-drop preparation shows that, in certain instances, the former method will indicate motility when the latter does not. The use of stab cultures was shown to be distinctly advantageous when only a small proportion of motile cells is present in a culture, for these may be missed entirely either in hanging-drop preparations or when the semi-solid medium is used poured in plates. The advantages of the semi-solid agar method are particularly evident in teaching schedules and routine testing.

SOLID EXTRACTS

By Ivor Griffith, Ph. M., Sc. D.

The penalties of "slimming", vary with the medicinals used. Thyroid, so long relied upon by rotund women, seeking streamline design, has more than frequently fashioned its victims to fit a very narrow coffin—long before their time. Dinitrophenol, picric acid's erratic chemical sister, is another slimming devil in disguise.

More than fifty young and middle-aged women who took this new and dangerous reducing medicine, dinitrophenol, developed cataract of the eye, Dr. Warren D. Horner of San Francisco reported at a recent medical meeting. The cataracts developed exactly as they do in elderly people. Within a few weeks all the victims can see is the movements of their hands. No treatment has been found to retard the growth of the cataracts, but extraction of the cataracts gives results comparable with this method of treating other kinds of cataracts.

And what is the good of girth control when one is reduced to a senile blindness?

When Fido licks his wounds, he is not making an organoleptic diagnosis—he is just applying a home-made antiseptic lotion.

Licking their wounds, a practise universal among animals, has good bacteriological justification, Dr. Herman Dold, professor of hygiene at the University of Tübingen, has found. Cultures of bacteria to which animal saliva was added failed to thrive, while untreated "control" cultures grew flourishing colonies of the germs. It therefore appears likely that in addition to keeping dirt and hair out of their wounds by the constant licking, the afflicted animals are also applying an effective antiseptic. A case of salvation by salivation.

Allergy, according to a definition recently given in a nurses' examination is "neither allegory nor algebra, but something else"—a

definition to which all hay fever sufferers will subscribe. Pollinosis (the highbrow name for hay fever) and not derived from pollen *and* noses, *is only one form of allergy. There are hundreds of comestibles, etc., which "are one man's food and another man's poison." Milk, for instance, can prove highly disturbing to persons displaying a special antipathy to it. But here is a piece of news for persons so afflicted.*

A milk which sensitive or allergic infants and grown persons, who break out into an eczema-like rash every time they drink ordinary milk, could imbibe without any ill effects is described in a patent granted to W. O. Frohring, of Shaker Heights, Ohio.

Giving milk a special heat treatment, the inventor has found, seems to eliminate or reduce the allergy-inducing tendencies of these proteins.

In applying this heat treatment, ordinary pasteurized milk is first poured into containers which are then sealed to keep air out. The sealed milk is then heated to a temperature of between 240 and 242 degrees Fahrenheit for about two hours. That is all there is to the process. The treatment kills spores and bacteria, and more important, without any apparent breakdown of the proteins, it changes them so that the milk becomes safe for milk-allergic persons to drink.

When Doctor Brown writes a prescription at the bedside of a patient suffering from a virulent septic disease—is it possible that the prescription itself may carry to the compounder the very disease it seeks to combat?

Yes! according to Dr. Kosowski, of Warsaw (*Pharm. Jour.* London, 1935, p. 135).

Dr. Kosowski found that there was a marked difference in the dangers, depending upon the kind of paper upon which the prescriptions were written.

Straw cellulose paper carried more germs than wood pulp; paper with gelatin and starch as an ingredient was distinctly favorable to the growth of micro-organisms; but if vegetable mucilage was an ingredient the micro-organisms did not thrive.

He examined 360 prescriptions, which he had collected from various pharmacies in Warsaw and found they were all contaminated with various dangerous organisms.

Of course, dollar bills or any other bills, carry the same possibility, excepting that that they pass through many more hands than the prescriptions.

Anyhow—germs or no germs—prescriptions and dollar bills are altogether too scarce.

"Don't get excited!"—is good medical advice although it may come more frequently from non-medical sources. If our blood volume acts, in us, as it does in rabbits and cats, we actually do vent our spleen when we are cross. The specific gravity of blood is greater during excitement than when one is calm, and the spleen, a red blood cell factory in the body, is partially responsible, recent experiments by Drs. L. B. Nice and H. L. Katz, of Ohio State University, show.

The two scientists have been studying the effects of excitement on rabbits and cats. In normal animals the increase in specific gravity of the blood after they had been excited was quite marked, but in rabbits whose spleens had been removed this increase was much smaller.

Actually the specific gravity is raised by water withdrawal, as well as by a squeezing of red cells from the spleen into active circulation.

Since the red blood corpuscles carry oxygen from the lungs to points where it is needed, this makes more oxygen available to the muscles, nerves, and glands so that it is possible to act more quickly and more forcibly in response to whatever it is that is producing the fear, rage, or other emotion.

Hats off to chlorine! The little typhoid bug that once held sway in cities, has certainly gone rustic. The spigot in the city kitchen no longer harbors the pest, and the old oaken bucket that hangs in the well is to the sanitarian as pernicious as it was romantic to the poet who sang its praises. Chlorination of municipal waters has practically eliminated this disease, once so prevalent among urban residents. And there are still those goofs who deplore the taste, that chlorine occasionally confers upon water.

But listen, twenty-four large cities have a place on the honor roll of the American Medical Association, having had no deaths from

typhoid fever during the year 1935. (*Journal, American Medical Association,* June 6.)

These cities are: Bridgeport, Conn.; Cambridge, Mass.; Elizabeth, N. J.; Erie, Pa.; Fort Wayne, Ind.; Grand Rapids, Mich.; Jacksonville, Fla.; Jersey City, N. J.; Long Beach, Calif.; Milwaukee, Wis.; Newark, N. J.; New Bedford, Mass.; New Haven, Conn.; Omaha, Neb.; Paterson, N. J.; Peoria, Ill.; San Diego, Calif.; Scranton, Pa.; Somerville, Mass.; Springfield, Mass.; Tacoma, Wash.; Trenton, N. J.; Wichita, Kans., and Youngstown, Ohio.

Eight of these cities—five of them in New England—had no deaths either from typhoid or diphtheria in 1935. They are: Bridgeport, Cambridge, Erie, New Bedford, New Haven, Scranton, Springfield and Tacoma.

And now comes science to take the wind out of the sails of Popeye, the spinach man. The leafy vegetable, obnoxious to many and eaten often only because of its widely heralded health value, is losing its high standing, discussions at the recent session of the American Institute of Nutrition revealed.

Spinach has been considered a valuable food because it has a high content of blood-and-bone-building iron and calcium. Less than half of the iron content of spinach, however, and less than a third of its calcium are in a form that can be used by the body, it appears from a report by Yale University workers.

Similarly, the amount of protein available for human nutrition is not what would be thought from the amount found in spinach by analysis.

In their research, the Yale investigators devised a method which in the future can be used for determining in other foods besides spinach the amount of nourishing substances actually available to the body, as compared with the amount theoretically available as judged by the total content of these substances found in foods by analysis.

Pepsin, the unorthodox porcine enzyme, is frequently prescribed in five grain doses. Even if it were of the 1:3000 variety, such a dose would theoretically convert over two pounds of proteins into assimil-

able, simpler amino-acid aggregates. The same amount of the newer 1:10,000 pepsin would change a seven pound chicken to soup or jelly. In other words, such large doses of pepsin seem hardly justified. Pancreatin from malt, however, is frequently prescribed in such small doses that one wonders how it can be expected to function, at least in a starch converting direction, since its digesting ratio is only 1 to 25. Insulin, on the other hand, seems to lend itself to more sensible unit dose control and yet the new compound protamine insulin is heralded as providing a prolongation of action not heretofore available.

This new kind of insulin was developed by Danish scientists. It was not intended to supplant ordinary insulin in cases of diabetes which can be satisfactorily controlled by insulin alone, but was found a valuable adjunct to insulin in treating cases of severe diabetes. Protamine insulin is relatively insoluble and tends to be absorbed slowly and over a longer period of time than ordinary insulin. Consequently its blood sugar lowering effect lasts longer—twice as long, in fact.

Late

"If we could emulate Noah and review a Parade of the Animal Kingdom containing a pair of every species of animal known to science, and if these animals were to march by at the rate of one pair every three seconds, more than a month would elapse before the Gorilla would make his appearance. No one knows how many different kinds, or species, of animals are now living on the earth, but three million is certainly a conservative estimate."—Robert Hegner in *Parade of the Animal Kingdom* (Macmillan).

BOOK REVIEW

DIGITALIS. Dr. H. Weese, instructor of pharmacology at the University of Cologne, and Director of the Pharmacological Institute of the I. G. Dye Industry (Elberfeld), Germany, collected detailed data on digitalis in a book with 296 pages, an excellent title picture of Withering and 72 text illustrations. Mk. 26.-, published in German by G. Thieme. Leipzig, 1936.

It represents the first of the series of monographs for pharmacology and experimental therapy, aiming at the discussion, both of the present state of our knowledge, inclusive of the methods used to obtain the facts, as well as the problems in need of solution. The directors of this series thus hope to assist the workers in medical science in their task and to inspire new workers to join in further research.

The author, with the assistance of experts in their special fields, referred to in the preface, has, we feel, contributed a remarkable survey. This surely will serve for a better understanding of the many intricate problems dealing with digitalis, chemically and clinically.

The wealth of data are enumerated in eight chapters, dealing in chapter 1: with the history of digitalis and strophantus glucosides; in chapter 2: with chemical and biological methods of evaluation; in chapter 3: with digitalis and related cardiac drugs, their botanical characteristics and chemical composition; in chapter 4: with the chemistry of digitalis glucosides with essentially known constitution; in chapter 5: with the biochemistry of digitalis glucosides; in chapter 6: with the special pharmacological effect; in chapter 7: with tabulated data concerning the pharmacology and toxicology of cardio-active glucosides; in chapter 8: with the therapy and dosage of digitalis treatment of man. A bibliography is appended to every chapter; an author and a detailed subject index concludes the volume.

Weese disclaims the purpose, in his critical survey, of duplicating the recent exemplary literary work of Lendle, who enumerated in a supplement volume of Heffter's handbook of experimental pharmacology the essential facts, presented in the world literature, on digitalis substances and related cardioactive glucosides.

It must be most gratifying to biochemists, physicians and pharmacists that we have thus available historical as well as most recent data, supplementing each other, on digitalis, one of our most important drugs. Weese has set in his monograph a worthy example of painstaking, intelligent work. Its consultation,—in immediate clinical use, in the preparation of extracts of glucosides, or in further studies, cannot but help to benefit ultimately those unfortunate millions suffering with temporary or permanent afflictions of the heart.

ARNO VIEHOEVER.